PATENT COOPERATION TREAT -

From the INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(date/month/year)* 19 November 2004 (19-11-2004)

Applicant's or agent's file reference	FOR FURTHER ACTION
13664-40PCT	See paragraph 2 below

International application no	International filing date *(date/month/year)*	Priority date *(date/month/year)*
PCT/CA2004/001409	26 July 2004 (26-07-2004)	25 July 2003 (25-07-2003)

International Patent Classification (IPC) or both national classification and IPC

IPC[7] C07K-14/62, C07K-14/765, A61P-10, C07K-1/113, A61K-38/28, A61-5/50

Applicant CONJUCHEM, INC. ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. 19/FEB/2005

25/MAY/2005
Reply to Written Opinion
DUE ON MAY 25 2005 NA

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/	Authorized officer
Commissioner of Patents	Colleen MacFarlane (819) 997-4614
Canadian Patent Office	

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

[ ] This opinion has been established on the basis of a translation from the original language into the following language __ , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

[X] a sequence listing

[ ] table(s) related to the sequence listing

b. format of material

[X] in written format

[X] in computer readable form

c. time of filing/furnishing

[ ] contained in the international application as filed.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority for the purposes of search.

3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

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Box No. II Priority

1 [ ] The following document has not yet been furnished :

[ ] copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

[ ] translation of the earlier application whose priority has been claimed (rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2 [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purpose of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

The priority documents furnished were not available to the ISA at the time the written opinion was established. This opinion has nevertheless been established on the assumption that the relevant dates are the claimed priority dates.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claims Nos. 24-32

because

[X] the said international application, or the said claims Nos. 24-32 relate to the following subject matter which does not require an international preliminary examination *(specify)* :

Claims 24-32 are directed to methods of treatment of the human/animal body. (Article 34(4)(a)(i) and Rule 67.1(iv) PCT)

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ___ are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. ___ are so inadequately supported by the description that no meaningful

[X] no international search report has been established for said claims Nos. 24-32 .

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form	[ ]	has not been furnished
	[ ]	does not comply with the standard
the computer readable form	[ ]	has not been furnished
	[ ]	does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1 [ ] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

[ ] paid additional fees

[ ] paid additional fees under protest

[ ] not paid additional fees

2 [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3 This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

[ ] complied with

[ ] not complied with for the following reasons :

4 Consequently, this opinion has been established in respect of the following parts of the international application :

[ ] all parts

[ ] the parts relating to claims Nos. ____

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY	International application No. PCT/CA2004/001409

Box No. V reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	4-6, 8-15	YES
	Claims	1-3, 7, 16-23, 33-38	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-23, 33-38	NO
Industrial applicability (IA)	Claims	1-23, 33-38	YES
	Claims		NO

2. Citations and explanations :

D1: WO 95/05187 A1 (UNITED MEDICAL & DENTAL SCHOOLS OF GUY'S AND ST. THOMAS' HOSPITALS)

D2: CA 2334859 A1 (KINGS COLLEGE LONDON; DEUTSCHES WOLLFORSCHUNGS INSTITUT)

D3: JONASSEN ET AL. "Fatty acid acylated insulins display protracted action due to binding to serum albumin." PEPTIDE SCIENCE: PRESENT AND FUTURE PROCEEDINGS OF THE INTERNATIONAL PEPTIDE SYMPOSIUM, 1st KYOTO, NOV. 30 1997 (1999), MEETING DATE 1997, pages 674-677. EDITOR: SHIMONISHI, YASUTSUGA. PUBLISHER: KLUWER, DORDRECHT, NETH.

D4: BAUDYS ET AL. "Extending insulin action *iv vivo* by conjugation to carboxymethyl dextran." BIOCONJUGATE CHEM. 1998, vol. 9, pages 176-183.

D5: CA 2363712 A1 (CONJUCHEM INC.)

D6: UCHIO ET AL. "Site specific insulin conjugates with enhanced stability and extended action profile." ADVANCED DRUG DELIVERY REVIEWS 35 (1999) vol. 35(2, 3), pages 289-306.

D7: US 6323311 B1 (LIU ET AL.)

D8: US 3868357 A (SMYTH ET AL.)

D9: US 3868356 A (SMYTH ET AL.)

D10: THIBAUDEAU ET AL. "Development of novel DAC™ insulin analogues with extended pharmacodynamic profiles." AMERICAN DIABETES ASSOCIATION 64TH SCIENTIFIC SESSIONS. ABSTRACT 488-P, June 4-8, 2004, ORLANDO, FLORIDA

1. NOVELTY

The instant alleged invention as claimed broadly is a derivatized insulin which has a reactive group which can bind a blood component so as to prolong insulin activity. In its preferred embodiment, the insulin is derivatized at positions Gly A1, Phe B1 or Lys B29 with a succinimidyl-containing group, a maleimido-containing group or a Michael acceptor.

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Box No. VI **Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

The description contravenes Rules 5.1(a)(ii) and 5.1(a)(iii) (PCT) as no background art is cited which could be useful for the understanding, searching and examination of the invention and the technical problem and solution have not been discussed with reference to the background art.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim 12 should not depend on claim 6 as there is no antecedent for "linker" in claim 6 (Article 6 (PCT)).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Box V (2)

Document D10 is not considered in this opinion based on the assumption of valid priority. If on the other hand, the priority dates are confirmed to lack validity, then D10 would be considered as novelty-destroying.

i) Document D1 discloses insulin analogues comprising insulin or a functional equivalent thereof conjugated to a pendant molecule at the B1 residue which has an affinity for binding proteins in blood plasma. Thyroxine is exemplified as a pendant molecule conjugated to insulin, allowing the analogue to bind to thyroxine binding proteins (TBP), which are blood components and include albumin (p. 10 line 26). The analogues may also contain spacer or linker molecules of 3-10 carbons. These analogues can be used as replacement for insulin therapy or to treat glycaemic-related diseases. Claims 1, 2, 7, 16-23, 33-38 are therefore considered to lack novelty under Article 33(2) PCT in light of the disclosure of document D1.

ii) Document D2 is considered novelty-destroying for claims 1-3, 7, 16, 18, 19, 21-23 and 33-38 while document D3 anticipates claims 1-3, 7, 16-23 and 33-38 under Article 33(2) PCT. D2 discloses an insulin analogue comprising insulin conjugated to 3,3',5-triiodothyroxine at the B1 position allowing for binding with thyroxine binding proteins. D3 discloses the acylation of insulin at the B29 position by fatty acids allowing binding to serum albumin and its use in the treatment of diabetes. As both of these documents disclose derivatized insulin molecules capable of binding blood components which result in protracted insulin activity and their uses in the treatment of glycaemic-related conditions, the aforementioned claims cannot be considered as novel.

iii) Document D4 discloses an insulin conjugate comprising carboxymethyl dextran (CMD) attached to Gly A1 of insulin which allows the binding of 3-4 insulin molecules to one CMD chain so as to stabilize and prolong insulin action. As insulin itself is a blood component, claims 1-3, 7, 16, 18, 19, 21-23 and 33-38 are considered to lack novelty under Article 33(2) PCT.

iv) Claims 4-6 and 8-15 are considered to be novel under Article 33(2) PCT as the prior art does not fairly suggest the claimed compounds.

2. INVENTIVE STEP

The problem to be solved is the extension of the half life of insulin so as to prolong its activity and reduce the number of injections necessary to maintain blood glucose levels in glycaemic-related conditions. CA 2363712 (D5) discloses a method of derivatizing insulinotropic peptides (GLP-1 and exendin 3 and 4) with reactive groups (maleimido and succinimidyl) with or without a linker so as to bind blood components for the purpose of prolonging the insulinotropic activity. In addition, it is well known in the art (for example D6, D7, D8, D9 as well as D1, D2 and D3) that the amino acid positions Gly A1, Phe B1 and Lys B29 are the reactive sites on the insulin molecule and the positions at which insulin can be derivatized. It would have been entirely within the competence of a skilled technician to use the methods disclosed in D5 to derivatize insulin with the same reactive groups (eg. maleimido and succinimidyl) at the A1, B1 and B29 positions using the techniques disclosed in the aforementioned references and expect the derivatized insulin and the insulin conjugated to a blood component to result in insulin with prolonged activity. Claims 1-23 and 33-38 therefore cannot be considered as involving an inventive step under Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY

Claims 1-23 and 33-38 are considered to have industrial applicability under Article 33(4).